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doi:10.1016/j.jtcvs.2009.12.053

Reply to the Editor:

We thank our colleagues Cheng and associates for their commentary with regard to our recently published article, ''The Sentinel Node Concept in Adenocarcinomas of the Distal Esophagus and Gastroesophageal Junction.''[1] In this study, we used the widely recognized immunohistochemical assay in which antibodies against epithelial-cell proteins are used to detect small clusters of tumor cells in histologically node-negative lymph nodes of patients with esophageal adenocarcinoma. Yao and Han claim that the monoclonal antibody against cytokeratin 8 and 18 (clone NCL-5D3) that we used in the present study should not be mistaken with the CAM5.2 antibody (clone CAM5.2) that appears to be specific for cytokeratin 7 and 8. In our article, we stated that the used antibody CAM 5.2 is specific for intracellular cytokeratin 8 and 18, referring to the original paper of Makin, Bobrow, and Bodmer,[2] in which it is claimed that (at that time newly developed) antibody CAM5.2 identifies the lower molecular weight cytokeratins (cytokeratin 8, 18 and 19). Other studies that investigated the presence and relevance of micrometastases or isolated tumor cells by using antibody CAM5.2 have also referred to this article.[3] However, over the last years, companies producing these antibodies have changed their products and further investigated the corresponding specificity in reactivity against certain cytokeratins, as pointed out by Yao and Han. Therefore, their statement that antibody CAM5.2 is not specific for intracellular cytokeratin 8 and 18 is correct. Nevertheless, this finding does not affect the conclusions of our study. The presence of cytokeratin 8 and/or 18 (which are both expressed in esophageal adenocarcinoma[4]) as detected with the antibody used in our study (clone NCL-5D3) indicates epithelial cell deposits in lymphoid tissue. Therefore, these cytokeratin deposits will still imply the presence of micrometastatic disease.

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doi:10.1016/j.jtcvs.2010.03.004

ANGIOGENESIS AND SURGICAL OR ENDOVASCULAR ENHANCEMENT OF NONCORONARY COLLATERAL CIRCULATION: A NEW RESEARCH FIELD

To the Editor:

We read with great interest the article by Atluri and colleagues,[1] and we congratulate them for their experiments with myocardial perfusion and contractility improvement using a laser transmyocardial approach. We agree with the authors that the problem with myocardial revascularization in patients who might not benefit from conventional procedures still demands investigative efforts. This was the genesis of a research program we began at Laval University in Quebec and that we are going to start in Europe at Université Paris Sud. This program is aimed at the enhancement of noncoronary collateral circulation (NCCC). Our animal models are dogs (Canada) and pigs (France).

NCCC is a topic that is virtually ignored, with very few publications in existence. This is surprising, considering that it is not rare to find evidence of NCCC, such as during coronary bypass surgery when arterial blood flow comes from the coronary ostia during valve replacement surgery or from the incised coronary artery, despite adequate aortic crossclamping and venting. NCCC consists of a network of small channels that come from mediastinal, bronchial, and pericardial vessels and that enter the heart through the pericardial reflections surrounding the pulmonary and systemic veins, as well as through the vasa vasorum of the aorta and pulmonary artery leading to and from the myocardium. Our studies are premised on the belief that this network is bigger than generally thought and that it might play a role, if adequately enhanced, as an alternative means of myocardial blood supply. We also believe that the normal ventricular function sometimes seen in patients with occlusion of the 3 major coronary vessels can be evidence of myocardial nourishment related to such a collateral source. Previous studies[2] have shown that vascular connections exist between the internal thoracic arteries (ITAs) and myocardium and that surgical bilateral ligation of the ITAs creates a local hypertensive status, increasing the perfusion pressure within the channels leading to the heart.[3]

Before cardiopulmonary bypass became widespread, some groups in Italy[2] and the United States[3] performed ligation of the ITAs in canine models and human subjects with ischemic heart disease. Reported results were promising: angina disappeared, correlating with the disappearance of ischemic signs at electrocardiography. We believe that these data should be re-explored with the help of modern technology. Our hypothesis[4,5] has been that administration of angiogenic growth factors combined with distal occlusion of the ITAs might enhance angiogenesis of NCCC. We performed surgical ligature of the ITAs distally, and vascular endothelial growth factor was administered into the occluded arteries. Intuitively, occlusion by means of endovascular embolization is possible as well. It is known that the ITAs have high plastic potential, being capable of developing major branches that work as the only source of blood in extreme cases of lower limb ischemia.[6] Hence myocardial ischemia should also be able to stimulate noncoronary collateral blood flow, preferably diverting this to the diseased area rather than to the chest wall.

It will be neither easy nor quick to demonstrate such theories, but our current studies represent a parallel, alternative research field, moving in the same direction of laser transmyocardial revascularization.

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doi:10.1016/j.jtcvs.2010.02.047

Reply to the Editor:

With great interest, we read Picichè and associates' letter entitled, ''Angiogenesis and surgical or endovascular enhancement of noncoronary collateral circulation: a new research field.'' We thank the authors for their kind comments regarding our article on the neovasculogenic effects of transmyocardial revascularization. We agree wholeheartedly with the authors that in patients with coronary artery disease, noncoronary collateral circulation and the microvasculature comprise critical components of myocardial perfusion and viability and hence greatly affect cardiomyocyte and ventricular function. Although surgical and percutaneous coronary therapy and investigative research are focused predominantly on large epicardial coronary vessels, the small collaterals and microvasculature are greatly underappreciated and understudied.

Certainly there are abundant clinical anecdotes of patients surviving on various permutations of coronary and noncoronary collaterals. Clinicians have all encountered the patient with an angiographically absent major coronary artery yet with the subtended myocardium demonstrating completely normal contractility on echocardiographic analysis. Is such a large region supplied through coronary collaterals, noncoronary collaterals from the base of the heart and posterior pericardial reflection or perhaps through the highly vascularized adhesions that surgeons encounter when operating on patients with prior cardiac surgery, renal failure, or myocardial infarction and Dressler syndrome? In older patients and in states of chronic disease, the ability to generate such collaterals can be impaired.[1,2] Researchers are beginning to understand the critical interrelated roles of endogenous myocardium-mediated proangiogenic signaling and bone marrow–derived endothelial progenitor cells.[3,4] Although initially very promising, the results of clinical trials aimed at harnessing this intrinsic revascularization machinery have been clinically equivocal.[5-7] Perhaps what is needed is a refocus on augmenting noncoronary collaterals as an additional driving force in therapeutic neovascularization.

The authors present a very intriguing strategy of ligating both distal internal thoracic arteries to produce a regional state of hypertension and hyperperfusion around the mediastinum. Coupled with local delivery of angiogenic cytokines, the authors propose to enhance the development of noncoronary collaterals to reperfuse the ischemic myocardium in 2 large animal models. The preliminary background data presented by the authors is encouraging. Although critics will focus on the preclusion of a future left internal thoracic artery–left anterior descending coronary artery graft, the cornerstone of coronary artery bypass grafting